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EXAMINER	
HA, JULIE	
ART UNIT	PAPER NUMBER
1654	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,169	NEW, ROGER R. C.	
	Examiner	Art Unit	
	JULIE HA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-7,9-14,19-24 and 26-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-7,9-14,19-24 and 26-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/29/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Non-final rejection filed on November 5, 2008 is acknowledged. New claims 36-38 have been added. Claims 1-2, 5-7, 9-14, 19-24, 26-38 are pending in this application. Claims 1-2, 5-7, 9-14, 19-24 and 26-38 are examined on the merits in this office action.

1. The declaration under 37 CFR 1.132 filed November 05, 2008 is insufficient to overcome the rejection of claims 1-2, 5-7, 9-14, 19-24 and 26-38 based upon 35 U.S.C. 103(a) as set forth in the last Office action because the declaration is missing the following statement. The MPEP states the following: The declaration must include an acknowledgment by the declarant that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. 1001) and may jeopardize the validity of the application or any patent issuing thereon. The declarant must set forth in the body of the declaration that all statements made of the declarant's own knowledge are true and all statements made on information and belief are believed to be true." (see MPEP 715.04 [R-6] II).

Withdrawn Rejection

2. Claims 1-2, 5-7, 9-14, 19-24 and 26-35 rejected under 35 U.S.C. 112, 2nd as being indefinite is hereby withdrawn in view of Applicant's persuasive argument.

Maintained Rejections

35 U.S.C. 112, 2nd

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 9-11 and 19-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims recite, "...and derivatives and analogues thereof, either synthetic or from natural sources, conforming to structures derived from either human or animal origin..." This phrase is unclear. It is unclear what modifications are encompassed within the derivatives and analogues of the macromolecular principles, and what modifications are encompassed within derivatives or analogues conforming to structures derived from either human or animal origin.

Response to Applicant's Arguments

5. Applicant argues that "derivatives and analogues, either synthetic or from natural sources, conforming to structures derived from either human or animal origin [of insulin, etc], is a compound that might be considered to be a derivative of insulin in chemical term but is in reality completely inactive is not covered by the claims of the present application." Applicant further argues that "the active derivatives and analogues of insulin are both well known and a matter of public record." Additionally, Applicant argues that "The present invention is generally applicable to all macromolecules...it is clearly

appropriate simply to indicate that, although the present invention works well with insulin, there is no difficulty in using derivative or analogue of insulin instead."

6. Applicant's arguments have been fully considered but have not been found persuasive. There are vast numbers of different growth hormones that have different amino acid content. A search of growth hormone on NCBI database yield 4365 different growth hormone from different species. For example, GenBank Accession No. CAA54461 teaches a growth hormone from *Coregonus autumnalis* that is 210 amino acids in lengths (see enclosed); Growth hormone from *Equus caballus* (GenBank Accession No. NP_001075417) teaches a 216 amino acid in lengths sequence (see enclosed). Furthermore, parathyroid hormone also has multiple sequences. For example, GenBank Accession No. AAA72730 disclose a 144 amino acid residue sequence. A derivative or analog of parathyroid hormone can be any sequence variance of this wildtype sequence, or any addition, deletion or substitution or any mutation to this sequence. Therefore, there is vast number of derivatives and analogues of parathyroid that may be encompassed within the term. Furthermore, since the derivative or analogues may also be synthetic, it is unclear what modifications are encompassed within the derivatives or analogues conforming to structures derived from either human or animal origin.

35 U.S.C. 112, 1st

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 9-11 and 19-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872 F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims are drawn to an active macromolecular principle chosen from insulin, calcitonin, growth hormone, parathyroid hormone, erythropoietin,

GLP-1 and GCSF, and derivatives and analogues thereof, either synthetic or from natural sources, conforming to structures derived from either human or animal origin. The generic statements derivatives and analogues thereof, either synthetic or from natural sources, conforming to structures derived from either human or animal origin do not provide ample written description for the compounds since the claims do not describe a single structural feature. The specification does not clearly define or provide examples of what qualify as compounds of the claimed invention.

As stated earlier, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable claims 9-11 and 19-21 are broad generics with respect all possible compounds encompassed by the claims. The possible structural variations are limitless to any class of peptide or a peptide-like molecule that can form peptide or amide bonds to make the variants or derivatives of the class of macromolecular polypeptides. It must not be forgotten that the MPEP states that if a peptide is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of

derivatives, analogues and sequence variants of the polypeptides. The specification is void of organic molecules that functions as a peptide-like molecule that qualify for the functional characteristics claimed as a peptide or a peptide-like molecule or other peptidic or peptidomimetic or amino acid mimetic molecules that can form peptide bonds to form peptide-like molecules, and other synthetic small molecules that can function as peptide-like molecules.

The specification discloses that polypeptides and proteins such as insulin, calcitonin, human serum albumin, growth hormone…erythropoeitins and EPO mimetics, colony stimulating factors including GCSF and GMCSF…GLP-1…enzymes including histone deacetylase, superoxide dismutase…collagen, elastin or fibronectin…antibody molecules…proteins or peptides containing antigenic epitopes and fragments, and derivatives, conjugates and sequence variants of any of the above (see pp. 3-4 of specification). The working examples describes insulin as active macromolecular principle (see Examples 1, 6 and 8-9); calcitonin as active macromolecular principle (see Example 7). The specification does not describe any of the derivatives, conjugates, sequence variants or analogues of the polypeptides described. Description of insulin and calcitonin is not sufficient to encompass numerous other proteins that belong to the same genus. For example, there are varying lengths, varying amino acid compositions, and numerous distinct qualities that make up the genus. For example, human calcitonin has 93 amino acid residues (see GenBank Accession No. CAA26189). A derivative of calcitonin can have amino acid substitutions, deletions or additions and other modifications along the amino acid sequences. There are 20 naturally occurring amino

acids, thus there are 93^{20} = 2.3 X 10^{39} different possibilities. When non-natural amino acids (such as D-isomers, β-amino acids, γ-amino acids, ε-amino acids and modified amino acids) are factored into the equation, the numbers are innumerable. For a larger macromolecular protein such as growth hormone (GenBank Accession No. AAA49464) having 200 amino acids, there are 200^{20} = 1.05 X 10^{46} different possibilities for naturally occurring amino acids alone. Therefore, the numbers of possibilities of derivatives, analogs or sequence variants of the polypeptides would increase according to the number of residues of that particular polypeptide. Therefore, there is not sufficient amount of examples provided to encompass the numerous characteristics of the whole genus claimed.

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate"). Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Response to Applicant's Arguments

9. Applicant argues that "in the present case, the Applicant has clearly demonstrated sufficient variety in the identity of the macromolecule. Thus, the application as filed included details of experiments conducted with two very different macromolecules, namely insulin and calcitonin, and both were shown to work." Applicant further argues that "insulin and calcitonin have no homology whatsoever. To name but a few differences, they possess completely different sequences, tertiary structures, isoelctric points and molecular weights....Given that success has been proven for two such different macromolecules, the skilled person would have no difficulty appreciating that the invention would work with e.g. derivative and analogues of insulin as well as it does with insulin."

10. Applicant's arguments have been fully considered but have not been found persuasive. The working examples describe insulin and calcitonin as active macromolecular principle. As Applicant has indicated, these two wild type principles have two different sequences, tertiary structures, isoelectric points and molecular weights. However, having these different genus modified to the derivatives and analogues having the same function could be innumerable. As described in the body of the rejection, the specification does not describe any of the derivatives, conjugates, sequence variants or analogues of the polypeptides described. Description of insulin and calcitonin is not sufficient to encompass numerous other proteins that belong to the same genus. For example, there are varying lengths, varying amino acid compositions, and numerous distinct qualities that make up the genus. For example, human calcitonin

has 93 amino acid residues (see GenBank Accession No. CAA26189). A derivative of calcitonin can have amino acid substitutions, deletions or additions and other modifications along the amino acid sequences. There are 20 naturally occurring amino acids, thus there are $93^{20} = 2.3 \times 10^{39}$ different possibilities. When non-natural amino acids (such as D-isomers, β-amino acids, γ-amino acids, ε-amino acids and modified amino acids) are factored into the equation, the numbers are innumerable. For a larger macromolecular protein such as growth hormone (GenBank Accession No. AAA49464) having 200 amino acids, there are $200^{20} = 1.05 \times 10^{46}$ different possibilities for naturally occurring amino acids alone. Additionally, for parathyroid hormone having 144 amino acid residues, this implies that there are $144^{20} = 8.37 \times 10^{22}$ different possibilities (GenBank Accession No. AAA72730). For any single, double or triple-stranded RNA, this also can have varying sequences, lengths, and characteristics. Therefore, the numbers of possibilities of derivatives, analogs or sequence variants of the polypeptides and RNA sequences would increase according to the number of residues of that particular polypeptide or RNA sequence. Therefore, there is not sufficient amount of examples provided to encompass the numerous characteristics of the whole genus claimed.

35 U.S.C. 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

13. Claims 1-2, 5-7, 9-14, 19-24 and 26-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over New (US Patent No. 5,853,748) in view of Desai (US Patent No. 5,206219) and Sonnenberg & Kotchen (Curr. Op. Neph. Hyperten., 1998, 7, 551-555). Please note that claims 19-24 were inadvertently omitted, but rejected in the body of the rejection below in the previous office action.

14. New teaches a pharmaceutical composition of (i) a biologically active proteinaceous material, oligonucleotide or analogue there of or polysaccharide; (ii) a bile acid or salt; and (iii) an agent having the ability to adjust the pH of the gut to a value of from 7.5 to 9 (see claim 1). New teaches specific example of macromolecular principle (insulin), a bile acid (chenodeoxycholic acid) and an additive that buffers the gut to pH 7.5-9 (sodium bicarbonate, example 4), meeting the limitation of claims 9-11 and 19-21. New teaches that sodium carbonate or bicarbonate can increase the solubility of the bile acids (see column 6, lines 4-7), and thus increase the permeability of bioactive through epithelial cells (see column 6, lines 4-19). New further teaches a composition with an enteric coating designed to prevent digestion in the stomach and to

permit digestion in the small intestine (see column 7, lines 37-40), meeting the limitation of claims 31-35. New teaches a method of enhancing the absorption of the insulin across the intestinal wall in an animal body comprising administering the insulin/chenodeoxycholic acid/sodium bicarbonate composition, meeting the limitation of claims 24, 26, 32 and 35. Further, the composition comprises less than 5% by weight of water (see table in example 4), meeting the limitations of claims 2 and 22. New teaches that the additive, sodium bicarbonate, is present at 8.3% by weight which is greater than 1% (table in Example 4). The ratio by weight of the chenodeoxycholic acid plus the additive to the insulin is 10:1 which is greater than 5:1 (table in Example 4). New teaches that the composition is in the form of a solution (see column 7, lines 5-55) or a solid (example 4), meeting the limitation of claims 6-7 and 23. The composition sensitizes the subject to insulin by increasing uptake (see example 4), meeting the limitation of claims 11 and 21. The non-conjugated bile acid is chenodeoxycholic acid, the acid form of chenodeoxycholate. New teaches that in general, bile salts start to be converted to their conjugate acid at pH of about 6.8 or below and the acid form is insoluble in aqueous solutions. New teaches that the buffering agent has the effect of buffering the compositions of the composition at a pH of about 7.5 or above, the solubilized bile salt will be present rather than the insoluble bile acid. A solubilized bile salt will be able to act on the epithelial cells when in solution, whereas this may not be possible in the solid acid form (see column 6, lines 6-14). Furthermore, New teaches that the higher the concentration of buffering agent, the more rapidly will a satisfactory pH be attained, resulting in more rapid dissolution of the bile acid or salt, resulting in a

higher local concentration of the bile salt in solution, leading to greater efficacy in enhancing permeability to bioactive materials (see column 6, lines 14-19). The reference further teaches that the composition is dispersed in water (see for example, claim 8), meeting the limitation of new claims 36-37. The difference between the reference and the instant claims is that the reference does not teach propyl gallate or butyl hydroxyl anisole (BHA) and further addition of insulin sensitizing agent.

15. However, Desai teaches that other adjuvants for preserving the formulations are common in pharmaceutical formulations and antioxidants like butylated hydroxyanisole (BHA), butylated hydroxytoluene, d-α-tocopherol, and propyl gallate are commonly used in pharmaceutical compositions of insulin and other protein active ingredients (see column 5, lines 5-18). Typical antioxidant concentrations can be used which is usually a standard practice; these can be from 0.1% to 1.5% (w/w or w/v). Desai further teaches a dosage unit pharmaceutical composition, adapted for oral administration, containing as active proteinaceous ingredients erythropoietin, insulin growth hormones, calcitonin, GCSF, cyclosporine, vasopressin or its agonists and antagonists…interferons or interleukins (see column 2, lines 13-18, and Examples 1-4).

16. Furthermore, Sonnenberg & Kotchen teach that troglitazone has been approved by the FDA for the treatment of type II diabetes. Sonnenberg & Kotchen teach that troglitazone produced a significant, dose-dependent reduction in glycosylated hemoglobin and fasting glucose concentrations despite decreases in insulin doses in clinical trials involving diabetic patients (see page 552).

17. It would have been obvious to one of ordinary skill in the art to add in antioxidants or preservatives, such as butyl hydroxyl anisole (BHA) or propyl gallate, since these additives are commonly used for preserving the pharmaceutical formulation, and prevent degradation, to enhance the longer shelf life of the proteinaceous ingredients. Furthermore, since New teaches the presence of sodium bicarbonate had beneficial effect by increasing the solubility of the bile acids to soluble bile salts and enhanced the permeability to bioactive materials (see New column 6, lines 4-7 and lines 17-19). Therefore, since New teaches the increased solubility of the bile acid or salt by sodium bicarbonate and teaches the pharmaceutical composition comprising an active macromolecule (insulin) and a non-conjugated bile acid or salt and sodium bicarbonate, it would have been obvious to add a well known antioxidant to preserve the pharmaceutical formulation. Since combination of sodium bicarbonate (additive) increased the solubility of the bile acid, then combination of a known antioxidant into the formulation would also have the same solubility. One of ordinary skill in the art would have been motivated to add in the antioxidants or preservatives to the pharmaceutical composition since these adjuvants would preserve the formulation, prevent degradation, and thus increase the shelf life of the pharmaceutical composition.

Further, it would have been obvious to one of ordinary skill in the art to maintain the pH of the intestinal fluid between pH 6.8 to 7.5, since New teaches that bile salts start to convert to its conjugate acid at pH of about 6.8 or below, and the acid form is insoluble in aqueous solution, and the buffering agent has the effect of buffering the compositions of the invention to a pH of about 7.5 or above, in which the solubilized bile

salt will be present rather than the insoluble acid. One would be motivated to maintain the pH of the intestinal fluid not above pH 7.5, since New teaches that the bile salts begin to be converted to their conjugate acid at pH of about 6.8 or below and the acid form is insoluble in aqueous solutions (see New column 6, lines 6-8). New additionally teaches that the pH of the gut is between 5 to7 (see column 4, lines 17-19). A solubilized bile salt will be able to act on the epithelial cells when in solution. There is a reasonable expectation of success, since the New reference teaches enhanced permeability of the bioactive agents by solubilizing the bile acids using the sodium bicarbonate, thus addition of an antioxidant (that prevents the degradation of peptide or protein in the pharmaceutical formulation) would also have the same solubility. Further, maintaining the intestinal fluid between pH 6.8 and 7.5 would allow the bile salt to be in the soluble salt non-conjugated form to act on the epithelial cells when in solution in the intestinal fluid, which will lead to greater efficacy in enhancing permeability to bioactive materials, such as insulin and other protein drugs.

Additionally, it would have been obvious to add a known insulin sensitizing agent in the pharmaceutical composition, since Sonnenberg & Kotchen teach that troglitazone has been approved by the FDA for the treatment of type II diabetes. One of the ordinary skilled in the art would have been motivated to add a known insulin sensitizing agent in the pharmaceutical composition, since Sonnenberg & Kotchen teach that troglitazone produced a significant, dose-dependent reduction in glycosylated hemoglobin and fasting glucose concentrations despite decreases in insulin doses in clinical trials involving diabetic patients. There would have been a reasonable expectation of

success, since the FDA has approved the use of troglitazone in combination with insulin, and has been shown to work in clinical trials involving diabetic patients.

In regards to instant claim 8 that recites, "A composition according to claim 1 wherein, when the composition is introduced into the intestine, the additive (c) enhances the solubility of the non-conjugated bile salt, the MPEP states the following: Furthermore, with respect to claim 8 which recites "wherein, when the composition is introduced into the intestine, the additive (c) enhances the solubility of the non-conjugated biloe salt" according to MPEP 2111.04: "Claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure. However, examples of claim language, although not exhaustive, that may raise a question as to the limiting effect of the language in a claim are:

(A) "adapted to" or "adapted for" clauses;

(B) "wherein" clauses; and

(C) "whereby" clauses.

The determination of whether each of these clauses is a limitation in a claim depends on the specific facts of the case. In *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329, 74 USPQ2d 1481, 1483 (Fed. Cir. 2005), the court held that when a "whereby' clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention." Id. However, the court noted (quoting Minton v. Nat'l Ass'n of Securities Dealers, Inc., 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003)) that a "whereby clause in a method claim is not given weight when it

simply expresses the intended result of a process step positively recited." Id. <". In the instant case, it is not deemed that the "wherein" clause limits the claim to particular structural features. Therefore, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Applicant's Arguments

18. Applicant argues that "adding PG or BHA to the '748 composition (i.e. without removing sodium bicarbonate), and then reduce the pH of the composition to somewhere in the region of 6.8 to 7.5 would result in an unworkable composition." Applicant argues that "The skilled person would clearly have been concerned with incompatibilities between PG/BHA and sodium bicarbonate in terms of solubility; one is an organic aromatic alcohol that is known to be hydrophobic, the other is an inorganic ionic compound...Moreover, compositions rendered unworkable by the addition of an incompatible additive such as sodium bicarbonate are clearly not envisaged in the present application. Thus, even if the skilled person had attempted to combine sodium bicarbonate and PG/BHA in the same composition, this would not have let to claim 1." Applicant further argues that "both PG and BHA have very poor solubility in water...thus, it is not credible to suggest that a skilled person would have thought to use them in compositions which are destined to be released in an aqueous environment, especially when the aim of the compositions is to achieve a concentrated but clear and proper

aqueous solution of the component." Applicant further argues that "there is no suggestion as to how to lower the pH of the sodium bicarbonate-containing composition…The '748 compositions have sodium bicarbonate specifically incorporated in them in order to buffer the pH of the environment to 7.5 to 9 when the composition is released in the gut…Solutions with sodium bicarbonate naturally achieve a pH of 8 to 8.5." Applicant further argues that "claim 1 does not need to recite that the PG or BHA enhances the solubility of the bile salt…It is a matter of empirical fact that PG and BHA do enhance bile salt solubility in the aqueous environment of the intestines."

19. Applicant's arguments have been fully considered, but have not been found persuasive.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., additive of PG and BHA enhance bile salt solubility in the aqueous environment of the instestines) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Additionally, the primary reference (New) teaches a pharmaceutical composition comprising an active macromolecular polypeptide (insulin), a non-conjugated bile acid or salt and an additive (sodium bicarbonate). The addition of sodium bicarbonate increased the solubility of the bile salt, thereby increasing the permeability of the bioactive agents across the cell wall. Therefore, addition of a well known antioxidant (preservative) would have the same solubility. Furthermore, it is well known in the

organic chemistry that sodium bicarbonates are added to amines to make the amine salts. Therefore, even though one is hydrophobic (amine) and one is inorganic compound (sodium bicarbonate), these two components have been known to be compatible and used together.

In regards to the argument that "the ability of the additives of claim 1 to exert this effect is unexpected because these additives have very poor solubility in water...moreover, while both are known antioxidants, their known use is preventing rancidity in oils and fats. The intestine, on the other hand, is an aqueous environment. Thus, no skilled person would have contemplated using BHA and PG in combination with non-conjugated bile acids and salts in an aqueous environment." Again, Applicant is reminded that claim 1 is drawn to a pharmaceutical composition. The primary reference (New) teaches a pharmaceutical composition comprising a macromolecular polypeptide (insulin), a non-conjugated bile acid or salt, and an additive (sodium bicarbonate) that increases the solubility of the non-conjugated bile acid, thus enhancing the permeability of the bioactive molecule. An addition of a well known antioxidant to the pharmaceutical composition that would preserve the formulation would have the same solubility, since the pharmaceutical composition having the sodium bicarbonate already increased the solubility of the bile acid. One of ordinary skill in the art would have been motivated to combine the well known antioxidant to the pharmaceutical formulation, since the secondary reference (Desai) teaches that these adjuvants preserve the pharmaceutical formulation, thus increasing the shelf-life of the proteinaceous bioactive agents. Since sodium bicarbonate increases the solubility, and

antioxidants are known to increase the shelf-life of the bioactive agents, one of ordinary skill in the art would have been motivated to use together, to achieve the optimal proteinaceous bioactive agent composition.

In regards to the argument that "in the present case, in order to achieve the special effects that New set out to provide in the '748 Patent, it is essential that the composition comprises 'an agent having ability to adjust the pH of the gut to a value of from 7.5 to 9' This is the crucial teaching of New...clearly removing the agent would rob the composition of New of its essential properties" it would have been obvious to maintain the pH of the intestinal fluid in between pH 6.8 and 7.5, since New teaches that "bile salts start to be converted to their conjugate acid at pH of about 6.8 or below and the acid form is insoluble in aqueous solutions." New further teaches that pH of the gut is between 5 to 7, therefore, one would have been motivated to maintain the pH of about 7, which includes 7.5. In regards to Applicant's argument that "to lower the pH from this range (pH of 8 to 8.5) would require the addition of such large amounts of other reagents that the formulation would be unfeasible," it would not take a lot of other agents to lower the pH from 8 to 8.5 to 6.8 to 7.5. Again, since the pH of the gut is between 5 to 7, it would have been obvious to one of ordinary skill in the art to maintain the pH of about 7.

The primary reference teaches that the additive is sodium bicarbonate, which increases the solubility of the non-conjugated bile acid or salt. Therefore, addition of well known antioxidants as preservative would have the same solubility. In regards to the argument that "in the present invention involves the use of aromatic alcohols (such

as the BHA and PG) in the aqueous environment of the intestine, in order to enhance the solubility of bile salts…there are a host of other known antioxidants that the skilled person would have been far more likely to consider. Desai teaches that other adjuvants for preserving the formulations are common in pharmaceutical formulations (see column 5, lines 6-7) and some of the oil soluble antioxidants listed are butylated hydroxyanisole, butylated hydroxytoluene, d-α-tocopherol, propyl gallate, etc (see column 5, lines 16-18). The examples show different biologically active peptides (see column 2, lines 13-18), such as insulin and d-α-tocopherol (part of the oil soluble antioxidant) (see Example 1); erythropoietin and d-α-tocopherol (see Example 2); human growth hormone and d-α-tocopherol (see Example 3); calcitonin and d-α-tocopherol (see Example 4). Therefore, one of ordinary skill in the art would have been motivated to use any of the oil soluble antioxidants listed. Further, the components (a) and (b) may already be in a solubilized form. There is no indication that (a) and (b) did not form a soluble formulation.

Conclusion

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). No claim is allowed.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. H./
Examiner, Art Unit 1654

/Cecilia Tsang/
Supervisory Patent Examiner
Art Unit 1654